IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Mountz, *et al.* §
ART UNIT: 1644

FILED: May 15, 1998 §

SERIAL NO.: 09/079,834 §
EXAMINER: Tung, M.

FOR: Fas Ligand Expressing Antigen Presenting Cells for Tolerance Induction §
DOCKET: D6005

Assistant Commissioner of Patents
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Washington, D.C. 20231

ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on January 31, 2000, and further in response to the Notification mailed March 24, 2000.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is the University of Alabama at Birmingham Research Foundation.

II. STATUS OF THE CLAIMS

Originally claims 1-17 were filed with this Application. Claims 10-15 were withdrawn from consideration. Claims 2 and 7 were canceled, and claims 1, 16 and 17 have been amended. Claims 8 and 9 were objected to. The pending claims 1, 3-6, 16 and 17 are being appealed, of which claims 1, 16 and 17 are independent claims.

III. STATUS OF AMENDMENTS

Claim 1 was amended in the Response to the Office Action of October 27, 1998. Claim 16 was amended in the Response to the Office Actions of April 21, 1999. Claim 17 was amended in the Response to the Office Action of October 27, 1998 and April 21,

1999. Subsequent to the final rejection mailed October 29, 1999, Applicants submitted a Response After Final which canceled claims 17, and added claims 18 and 19. In an Advisory Action mailed December 8, 1999, the amendments contained in the Response After Final were not entered into the record. All claims as pending are shown in Appendix A.

IV. STATEMENT OF RELATED APPEALS AND INTERFERENCES

To Applicant's knowledge, there are no pending related appeals or interferences which will directly affect or be directly affected by the present appeal.

V. SUMMARY OF THE INVENTION

The present invention is drawn to a method of inducing systemic tolerance to a viral or alloantigen using antigen presenting cells that express Fas ligand and the antigen, wherein said antigen presenting cells induce apoptosis of Fas-positive T cells directed towards said antigen resulting in induction of systemic tolerance to

said antigen (Specification, page 9, line 3-page 10, line 5). The present invention is also drawn to a method of using Fas ligand-expressing antigen presenting cells from a graft to create immune-privileged sites so as to decrease rejection of a graft (Specification, page 24, line 19-page 25, line 10).

VI. ISSUES

35 U.S.C. §102

Whether claim 17 is anticipated by **Bellgrau** et al. under 35 U.S.C. §102(e).

35 U.S.C. §103

Whether claims 1, 3-6 and 17 are unpatentably obvious under 35 U.S.C. §103(a) over **Bellgrau** et al. in view of **Süss** et al.

Whether claims 1, 3-6 and 17 are unpatentably obvious under 35 U.S.C. §103(a) over **Bellgrau** et al. in view of **Schuler** et al.

Whether claim 16 is unpatentably obvious under 35 U.S.C. §103(a) over **Bellgrau** et al. in view of **Süss** et al.

Whether claim 16 is unpatentably obvious under 35 U.S.C. §103(a) over **Bellgrau** et al. in view of **Schuler** et al.

VII. GROUPING OF CLAIMS

The rejected claims do not stand or fall together. Applicant considers claims 1, 3-6, 16 and 17 lie in three embodiments of the present invention. Claims 1 and 3-6 are drawn to a method of inducing systemic tolerance to a viral antigen, an autoantigen or an alloantigen using Fas ligand-expressing antigen presenting cells. Claim 16 is drawn to a method of creating immune-privileged sites so as to decrease transplant rejection. Claim 17 is drawn to a method of decreasing rejection of a graft.

VIII. ARGUMENTS

The Rejection Under 35 U.S.C. §102

In the Final Office Action mailed October 29, 1999, the Examiner maintained the rejection of claim 17 under 35 U.S.C.

§102(e) as being anticipated by **Bellgrau** et al. This rejection is respectfully traversed.

Bellgrau et al. teaches a method of suppressing T-lymphocyte-mediated rejection of transplanted tissue by implanting purified Fas ligand with pumps, wherein the diabetic rats are grafted with islet cells and implanted Fas ligand with a programmed pump (see Example 1). In **Bellgrau**'s method, the donor organ tissue, i.e., islet cells, and Fas ligand are introduced to the recipients through different routes and at different times. In contrast, Applicants' claim 17 recites a method of decreasing rejection of a graft by perfusing donor organ tissue with Fas ligand first and then introducing the donor organ tissue to the recipient. That is, the graft and Fas ligand are introduced to the recipient through the same route and at the same time.

Additionally, the method disclosed in the present invention uses donor tissue that has been engineered to not express Fas ligand. Moreover, the donor tissue provides antigen presenting cells which are capable of eliminating T cells specifically. That is, the present invention uses Fas negative antigen presenting cells. Perfused with the donor tissue, Fas ligand is targeted primarily to the spleen via antigen presenting cells and very seldom to the other

sites. This puts Fas ligand in the precise place where it induces a maximum benefit towards interaction with autoreactive T cells, resulting a systemic and not a local tolerance. In contrast, **Bellgrau** et al. teaches Fas ligand therapy in Fas positive cells. In their method, Fas ligand expression by Fas positive cells (i.e., donor tissue) is not protected but toxic and causes the apoptosis of the cells. Moreover, **Bellgrau** et al. does not teach antigen presenting cells or the expression of Fas ligand in the antigen presenting cells. Therefore, **Bellgrau**'s Fas ligand cannot be specifically targeted to the spleen but might migrate to the liver and other tissues and cause high toxicity.

In view of the above remarks, **Bellgrau** et al. does not teach each and every element of Applicants' claim 17 and, in fact, teaches away from the method of claim 17. Accordingly, Applicants request that the rejection of claim 17 under 35 U.S.C. §102(e) be withdrawn.

The Rejection Under 35 U.S.C. §103

In the Final Office Action mailed October 29, 1999, the Examiner maintained the rejection of claims 1, 3-6 and 17 under 35

U.S.C. §103(a) as being unpatentable over **Bellgrau** et al. in view of **Süss** et al. This rejection is respectfully traversed.

Bellgrau et al. teach a method of inhibiting T-lymphocyte-mediated immune responses by providing a recipient animal with Fas ligand or cells expressing Fas ligand. **Bellgrau** et al. do not teach the use of antigen presenting cells to express Fas ligand in said method.

Süss et al. teach that a sub-population of dendritic cells express Fas ligand and induce apoptosis of $CD4^+$ T cells which results in the down regulation of the immune response. The Examiner argued that one of ordinary skill in the art at the time the invention was made would have been motivated by the combined teaching of these two references and have reasonable expectation of success to use Fas ligand-expressing antigen presenting cells in methods of antigen-specific immunosuppression as disclosed in the instant invention.

However, in determining whether such a suggestion can be fairly gleaned from the prior art, the full field of the invention must be considered as a person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention. References

that teach away from the instant invention, i.e. showing Fas ligand expression did not lead to immunosuppression and prevention of graft rejection but rather induce an inflammatory response and accelerated graft rejection, were provided in the Specification (page 6, lines 16-20) and discussed in the Response After Final (**Kang** et al. and **Chen** et al.; enclosed). More specifically, high expression of Fas ligand can lead to immune cell infiltration and inflammation instead of immunosuppression. For example, **Kang** et al. disclosed that Fas ligand expression on pancreatic islets results in neutrophilic infiltration and accelerated graft rejection. **Chen** et al. disclosed subcutaneous injection of stably transfected colon carcinoma cells that express Fas ligand results in neutrophils activation and rejection of the cancer cells. Thus, expression of Fas ligand does not always inhibit immune responses. The fact that Fas ligand expression can lead to enhancement as well as inhibition of immune responses indicates that the regulatory function of Fas ligand is more complex and varies between different experimental and in vivo settings.

The effect of Fas ligand expression on an immune response also depends on the presence or absence of other regulatory factors in that particular site (**Chen** et al., page 1715, left column, lines 17-20). **Bellgrau** et al., however, only show

results with soluble Fas ligand and Fas ligand expressed on islet cells, which are not antigen presenting cells. **Süss** et al. only show data from in vitro culture. It is well known to a person hainvg ordinary skill in this art that one cannot always equate in vitro data to in vivo results. The differences between in vitro and in vivo situations becomes more important in view of the fact that **Chen** et al. teach that the in vivo microenvironment and the presence of secondary factor play an important role in regulating the effect of Fas ligand expression (see abstract; page 1715, left column, lines 17-20; page 1715, middle column, lines 1-4). Therefore, the combined teaching of **Bellgrau** et al. and **Süss** et al. does not address the potential problem of inflammation induced by Fas ligand expression, and the data in the combined references do not necessarily lead to the conclusion that Fas ligand expression on antigen presenting cells would lead to immunosuppression in transplantation or autoimmunity in vivo.

The Examiner did not respond to the argument Applicants made with regard to the cited references in the Response After Final. Applicants respectfully submit that in view of the cited references that lead away from the claimed invention, and secondly that there is no teaching or suggestion in the combined teaching of

Bellgrau et al. and Süss et al. that indicate the use of Fas ligand as disclosed in the instant invention would not lead to stimulation of immune response, the present invention is not *prima facie* obvious to one skilled in the art at the time the invention was made.

Moreover, there are aspects of Applicants' claimed invention which are neither taught nor suggested in the combined teaching of **Bellgrau** et al. and **Süss** et al. More specifically, the use of Fas negative antigen presenting cells derived from the mutant *lpr/lpr* mice, and the use of a two virus system to achieve a very high level of Fas ligand expression (specification page 10, line 6-page 11, line 2) are not disclosed by the cited references.

In the Final Office Action mailed October 29, 1999, the Examiner maintained the rejection of claims 1, 3-6 and 17 under 35 U.S.C. §103(a) as being unpatentable over **Bellgrau** et al. in view of **Schuler** et al. This rejection is respectfully traversed.

Bellgrau et al. teach a method of inhibiting T-lymphocyte-mediated immune responses by providing a recipient animal with Fas ligand or cells expressing Fas ligand. **Bellgrau** et al. do not teach the use of antigen presenting cells to express Fas ligand in the method.

Schuler et al. is a review article that only cited the reference of **Süss** et al. (page 320, right column, paragraph 2) to suggest tolerance induction in transplantation and autoimmunity by Fas ligand-expressing dendritic cells. **Schuler** et al. did not demonstrate a method of inducing antigen-specific systemic tolerance by administering antigen presenting cells expressing Fas ligand and the antigen.

Hence, the combined teaching of **Bellgrau** et al. and **Schuler** et al. is essentially the combined teaching of **Bellgrau** et al. and **Süss** et al. As discussed above, Applicants respectfully submit that in view of the literature cited by the Applicants and discussed above which leads away from the claimed invention, and secondly since there is no teaching or suggestion in the combined teaching of **Bellgrau** et al. and **Schuler** et al. that indicate the use of Fas ligand as disclosed in the instant invention would lead to immunosuppression rather than stimulation of immune response, the claims 1 and 3-6 is not *prima facie* obvious under 35 U.S.C. §103(a) to one skilled in the art at the time the invention was made.

In the Final Office Action mailed October 29, 1999, the Examiner maintained the rejection of claims 16 under 35 U.S.C.

§103(a) as being unpatentable over **Bellgrau** et al. in view of **Süss** et al., and unpatentable over **Bellgrau** et al. in view of **Schuler** et al. These rejections are respectfully traversed.

Claim 16 is drawn to a method of creating immune-privileged sites in an individual so as to decrease rejection of a graft by introducing Fas ligand into antigen presenting cells derived from the graft. The teaching of **Bellgrau** et al., **Süss** et al. and **Schuler** et al. were discussed *supra*.

Applicants respectfully submit that in view of the literature cited by the Applicants and discussed above which teaches away from the claimed invention, the references in **Süss** et al. that contribute Fas ligand expression in Sertoli cells and cells of the anterior chamber of the eye to the creation of immune-privileged sites at those tissues, and the mere speculation in **Schuler** et al. that Fas ligand-expressing dendritic cells may induce tolerance in transplantation do not enable one skilled in the art to successfully produce the claimed invention. As discussed *supra*, Fas ligand expression does not necessarily lead to immunosuppression and prevention of graft rejection but rather can induce an inflammatory response and accelerated graft rejection. Clearly, the effects of Fas ligand expression can vary greatly between different experimental

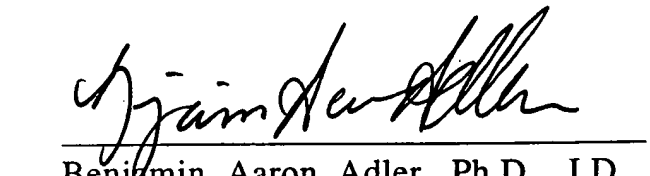
settings *in vivo*. Thus, teaching with concrete data in a similar experimental situation is critical for one skilled in the art to produce the claimed invention. However, there are no data in the combined cited references that show the effect of Fas ligand-expressing antigen presenting cells on graft survival *in vivo*.

In contrast, the instant invention disclosed detailed examination of alloantigen specific T cell tolerance using antigen specific transgenic mice (Examples 16-17). Hence, Applicants respectfully submit that the combination of the cited references would not provide a person having ordinary skill in this art with the requisite motivation nor expectation of successfully producing Applicants' claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by contrary references.

For the foregoing reasons, Applicant respectfully requests that the decision of the Examiner should be reversed, and that claims 1, 3-6, 16 and 17 be allowed.

Respectfully submitted,

Date: April 6, 2000



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CLAIMS ON APPEAL

1. A method of inducing systemic tolerance to an antigen in an individual in need of such treatment, comprising the step of:

administering antigen presenting cells to said individual, wherein said cells express Fas ligand and said antigen, wherein said antigen presenting cells induce apoptosis of Fas-positive T-cells directed towards said antigen resulting in said induction of systemic tolerance to said antigen.

3. The method of claim 1, wherein said antigen is selected from the group consisting of the adenovirus antigen, a viral antigen, an adeno-associated viral antigen, an autoantigen, and an alloantigen.

4. The method of claim 1, wherein said individual has an autoimmune disease.

5. The method of claim 4, wherein said autoimmune disease is selected from the group consisting of diabetes, multiple sclerosis, rheumatoid arthritis, thyroiditis, Grave's disease, systemic lupus erythematosus.

6. The method of claim 1, wherein said individual has had an organ transplant.

8. The method of claim 1, further comprising the step of delivering to said antigen presenting cells a gene to inhibit apoptosis.

9. The method of claim 8, wherein said gene to inhibit apoptosis is crmA.

16. A method of creating immune-privileged sites in an individual so as to decrease rejection of a graft, comprising the steps of:

extracting antigen presenting cells from donor organ tissue;

introducing Fas ligand into said antigen presenting cells to produce Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft;

introducing said Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft to said individual prior to and during said grafting procedure; wherein said Fas ligand-expressing antigen presenting cells expressing an antigen specific to said graft create said immune-privileged site at the site of said grafting procedure to prevent rejection of said graft in said individual.

17. A method of decreasing rejection of a graft in an individual, comprising the steps of:

perfusing donor organ tissue with Fas ligand; and

introducing the Fas ligand perfused donor organ tissue to said individual.